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=> d his

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     FILE 'REGISTRY' ENTERED AT 07:18:44 ON 01 OCT 2002
               E HBY-793/CN
L1             1 S E2

     FILE 'USPATFULL, CAPLUS' ENTERED AT 07:20:25 ON 01 OCT 2002

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L2            26 L1

=> dup rem l2
PROCESSING COMPLETED FOR L2
L3            26 DUP REM L2 (0 DUPLICATES REMOVED)

=> s l3 and (FIV or feline(2a)immunodeficien?(2a)vir?)
L4             2 L3 AND (FIV OR FELINE(2A) IMMUNODEFICIEN?(2A) VIR?)

=> d l4 abs ibib kwic 1 2

L4   ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2002 ACS
AB   Methods are provided for therapeutic and prophylactic treatment of cats
     against FIV infection.  Methods of the invention use a
     combination of antiretroviral compds. to treat or prevent FIV
     infection in a feline animal.  In one embodiment, the method comprises
     administering an effective amt. of AZT and another nucleoside analog, e.g.
     3TC, to the animal.  In another embodiment, cats are given an ED(s) of
     AZT, 3TC and a retroviral protease inhibitor.
ACCESSION NUMBER:         1999:763838  CAPLUS
DOCUMENT NUMBER:          132:431
TITLE:                    Combination therapy for treatment of feline
                          immunodeficiency virus (FIV
                          ) infection
INVENTOR(S):              Dunn, Ben M.; Yamamoto, Janet K.; Arai, Maki
PATENT ASSIGNEE(S):       University of Florida, USA
SOURCE:                   PCT Int. Appl., 28 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
     WO 9960988         A2   19991202       WO 1999-US11940  19990528
     WO 9960988         A3   20001207
         W:  AE, AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, GE, HR, HU,
             ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX,
             NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA,
             AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK,
             ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,
             CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     EP 1146882         A2   20011024       EP 1999-926027   19990528
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
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IE, FI
PRIORITY APPLN. INFO.: US 1998-87281P P 19980529
WO 1999-US11940 W 19990528

TI Combination therapy for treatment of **feline immunodeficiency virus** (**FIV**) infection

AB Methods are provided for therapeutic and prophylactic treatment of cats against **FIV** infection. Methods of the invention use a combination of antiretroviral compds. to treat or prevent **FIV** infection in a feline animal. In one embodiment, the method comprises administering an effective amt. of AZT and another nucleoside analog, e.g. 3TC, to the animal. In another embodiment, cats are given an ED(s) of AZT, 3TC and a retroviral protease inhibitor.

ST **FIV** antiviral combination nucleoside analog AZT; AZT 3TC
FIV antiviral combination; retrovirus protease inhibitor
FIV antiviral combination; **feline immunodeficiency virus** antiviral combination

IT Transplant and Transplantation
Transplant and Transplantation
(bone marrow; **feline immunodeficiency virus** combination therapy)

IT Antiviral agents
Drug interactions
Feline immunodeficiency virus
(**feline immunodeficiency virus** combination therapy)

IT Nucleoside analogs
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**feline immunodeficiency virus** combination therapy)

IT Retroviridae
(protease, inhibitors; **feline immunodeficiency virus** combination therapy)

IT Drug interactions
(synergistic; **feline immunodeficiency virus** combination therapy)

IT Radiotherapy
(total body irradn.; **feline immunodeficiency virus** combination therapy)

IT Bone marrow
Bone marrow
(transplant; **feline immunodeficiency virus** combination therapy)

IT 144114-21-6, Retropepsin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(HIV protease inhibitors; **feline immunodeficiency virus** combination therapy)

IT 30516-87-1, AZT 127779-20-8, Saquinavir 134678-17-4, 3TC
137755-25-0, HBY-793 150378-17-9, Indinavir
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**feline immunodeficiency virus** combination therapy)

L4 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2002 ACS

AB The design and synthesis of compds. targeted against human

immunodeficiency virus 1 (HIV-1) protease have resulted in effective antiviral therapies. However, the rapid replication of the virus and the inherent mutability of the viral genome result in the outgrowth of resistant strains in the majority of patients. Thus, there is a continuing need to develop new antiprotease compds. that may bind more effectively to the resistant forms of protease. This contribution examines the binding of a single inhibitor to two different retroviral proteases, HIV-1 protease and **feline immunodeficiency virus** protease. Despite the overall similarity of the related retroviral enzymes, specific substitutions within the binding site cavity provide a distinctly different binding landscape that dramatically alters the affinity of compds. Through this comparison, insights have been obtained into new strategies for drug design. New compds. based on these concepts have been tested against the two enzymes.

ACCESSION NUMBER: 1999:403908 CAPLUS
DOCUMENT NUMBER: 131:193737
TITLE: Comparison of inhibitor binding to **feline** and human **immunodeficiency virus** proteases: structure-based drug design and the resistance problem
AUTHOR(S): Dunn, Ben M.; Pennington, Michael W.; Frase, D. Constanza; Nash, Kevin
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, University of Florida College of Medicine, Gainesville, FL, 32610-0245, USA
SOURCE: Biopolymers (1999), 51(1), 69-77
CODEN: BIPMAA; ISSN: 0006-3525
PUBLISHER: John Wiley & Sons, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Comparison of inhibitor binding to **feline** and human **immunodeficiency virus** proteases: structure-based drug design and the resistance problem

AB The design and synthesis of compds. targeted against human immunodeficiency virus 1 (HIV-1) protease have resulted in effective antiviral therapies. However, the rapid replication of the virus and the inherent mutability of the viral genome result in the outgrowth of resistant strains in the majority of patients. Thus, there is a continuing need to develop new antiprotease compds. that may bind more effectively to the resistant forms of protease. This contribution examines the binding of a single inhibitor to two different retroviral proteases, HIV-1 protease and **feline immunodeficiency virus** protease. Despite the overall similarity of the related retroviral enzymes, specific substitutions within the binding site cavity provide a distinctly different binding landscape that dramatically alters the affinity of compds. Through this comparison, insights have been obtained into new strategies for drug design. New compds. based on these concepts have been tested against the two enzymes.

ST antiviral HIV **FIV** EIAV protease inhibitor; structure antiHIV antiFIV design drug resistance

IT Drug resistance
Structure-activity relationship
(antiviral; comparison of inhibitor binding to **FIV** and HIV proteases: structure-based drug design and the resistance problem)

IT Anti-AIDS agents
Crystal structure

Drug design
Equine infectious anemia virus
Feline immunodeficiency virus
Human immunodeficiency virus 1
Molecular modeling
(comparison of inhibitor binding to **FIV** and HIV proteases: structure-based drug design and the resistance problem)

IT **137755-25-0P**, HBY-793 153314-49-9P, LP-130 165074-99-7P, LP-149 240811-10-3P 240811-11-4P 240811-12-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(comparison of inhibitor binding to **FIV** and HIV proteases: structure-based drug design and the resistance problem)

IT 144114-21-6, Retropepsin
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(comparison of inhibitor binding to **FIV** and HIV proteases: structure-based drug design and the resistance problem)

=>

L6 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2002 ACS

AB A detailed structure-activity relation of C2-sym. diol inhibitors of **HIV**-1 protease leads to the inhibitor **HOE/BAY 793** which is very potent in the inhibition of the enzyme and in the inhibition of viral replication in **HIV** infected cell culture (IC50: 0.3 nM; EC50: 3 nM). There are well defined steric requirements for the design of the side chains P1-P3 of the inhibitors. In addn., all three side chains need to be lipophilic. While the enzyme tolerates hydrophilic substituents in some cases, drastic redns. in anti-**HIV** activity are obsd. in cell culture after substitution with hydrophilic groups, which is most likely due to insufficient cell penetration of these compds.

ACCESSION NUMBER: 1995:609444 CAPLUS
DOCUMENT NUMBER: 123:102047
TITLE: **HIV** protease inhibitor **HOE/BAY 793**, structure-activity relationships in a series of C2-symmetric diols
AUTHOR(S): Budt, Karl-Heinz; Peyman, Anusch; Hansen, Jutta; Knolle, Jochen; Meichsner, Christoph; Paessens, Arno; Ruppert, Dieter; Stowasser, Bernd
CORPORATE SOURCE: Hoechst AG, Pharma Res., Frankfurt, 65926, Germany
SOURCE: Bioorganic & Medicinal Chemistry (1995), 3(5), 559-71
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

TI **HIV** protease inhibitor **HOE/BAY 793**, structure-activity relationships in a series of C2-symmetric diols

AB A detailed structure-activity relation of C2-sym. diol inhibitors of **HIV**-1 protease leads to the inhibitor **HOE/BAY 793** which is very potent in the inhibition of the enzyme and in the inhibition of viral replication in **HIV** infected cell culture (IC50: 0.3 nM; EC50: 3 nM). There are well defined steric requirements for the design of the. . . all three side chains need to be lipophilic. While the enzyme tolerates hydrophilic substituents in some cases, drastic redns. in anti-**HIV** activity are obsd. in cell culture after substitution with hydrophilic groups, which is most likely due to insufficient cell penetration. . .

ST **HIV** protease inhibitor HOEBAY793 analog structure; HOEBAY793 analog prepn **HIV** protease inhibitor; antiviral **HIV** HOEBAY793 analog structure

IT Virucides and Virustats
(**HIV** protease inhibitor **HOE/BAY 793** and structure-activity relationships in a series of C2-sym. diol analogs in relation to antiviral activity in human cells)

IT Molecular structure-biological activity relationship
(aspartic proteinase-inhibiting, **HIV** protease inhibitor **HOE/BAY 793** and structure-activity relationships in a series of C2-sym. diol analogs in relation to antiviral activity in human cells)

IT Virus, animal
(human immunodeficiency 1, **HIV** protease inhibitor **HOE/BAY 793** and structure-activity relationships in a series of C2-sym. diol analogs in relation to antiviral activity in human cells)

IT Molecular structure-biological activity relationship
(virucidal, **HIV** protease inhibitor **HOE/BAY**

793 and structure-activity relationships in a series of C2-sym. diol analogs in relation to antiviral activity in human cells)

IT 137755-28-3P 165406-33-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(**HIV** protease inhibitor **HOE/BAY** **793** and structure-activity relationships in a series of C2-sym. diol analogs in relation to antiviral activity in human cells)

IT **137755-25-0P** 137755-42-1P 137755-47-6P 137755-48-7P 137808-03-8P 137808-09-4P 137808-16-3P 137821-89-7P 137828-14-9P 137828-15-0P 137828-18-3P 137828-21-8P 137828-24-1P 137828-27-4P 137828-32-1P 137828-36-5P 137828-38-7P 137853-70-4P 165406-34-8P 165406-35-9P 165406-37-1P 165406-39-3P 165406-40-6P 165406-41-7P 165406-42-8P 165406-43-9P 165406-44-0P 165406-45-1P 165406-46-2P 165406-47-3P 165406-48-4P 165406-51-9P 165406-52-0P 165876-29-9P 165876-32-4P 165876-34-6P 165876-35-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**HIV** protease inhibitor **HOE/BAY** **793** and structure-activity relationships in a series of C2-sym. diol analogs in relation to antiviral activity in human cells)

IT 144114-21-6, Retropepsin
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**HIV** protease inhibitor **HOE/BAY** **793** and structure-activity relationships in a series of C2-sym. diol analogs in relation to antiviral activity in human cells)

IT 2976-75-2, 1-Naphthyloxyacetic acid 13734-34-4, N-tert-Butoxycarbonyl-L-phenylalanine 13734-41-3, tert-Butoxycarbonyl-L-valine 17430-71-6 20312-36-1, S-Phenyllactic acid 61849-47-6 72155-45-4 122225-33-6 129491-63-0 137331-84-1 137755-38-5 137828-46-7 137828-50-3 137828-57-0 165406-36-0 165406-49-5 165406-50-8 165876-30-2 165876-33-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(**HIV** protease inhibitor **HOE/BAY** **793** and structure-activity relationships in a series of C2-sym. diol analogs in relation to antiviral activity in human cells)

IT 129491-64-1P 129491-65-2P 134805-49-5P 136740-96-0P 136740-98-2P 136740-99-3P 137755-20-5P 137808-10-7P 137808-17-4P 137828-43-4P 137828-44-5P 137894-61-2P 165406-30-4P 165406-31-5P 165406-32-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(**HIV** protease inhibitor **HOE/BAY** **793** and structure-activity relationships in a series of C2-sym. diol analogs in relation to antiviral activity in human cells)

IT 23402-69-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(protease inhibitor **HOE/BAY** **793** and structure-activity relationships in a series of C2-sym. diol analogs in relation to antiviral activity in human cells)

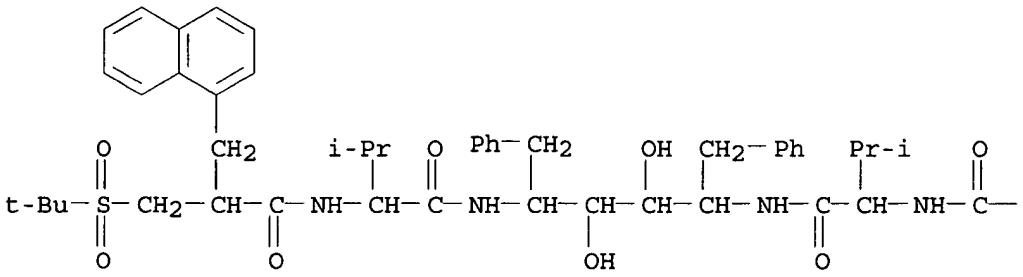
IT **137755-25-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES

(Uses)
(**HIV** protease inhibitor **HOE/BAY**
793 and structure-activity relationships in a series of C2-sym. diol analogs in relation to antiviral activity in human cells)

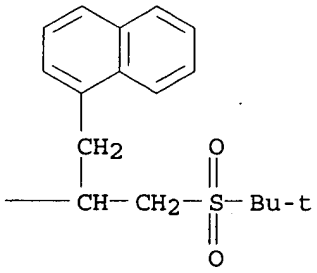
RN 137755-25-0 CAPLUS

CN L-Iditol, 1,2,5,6-tetradeoxy-2,5-bis[[(2S)-2-[[(2S)-2-[[(1,1-dimethylethyl)sulfonyl]methyl]-3-(1-naphthalenyl)-1-oxopropyl]amino]-3-methyl-1-oxobutyl]amino]-1,6-diphenyl- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 1-B



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FILE 'CAPLUS' ENTERED AT 00:17:42 ON 30 SEP 2002

FILE 'BIOSIS' ENTERED AT 00:17:42 ON 30 SEP 2002

FILE 'BIOBUSINESS' ENTERED AT 00:17:42 ON 30 SEP 2002

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L4 14 L3 AND (3TC OR PROTEASE(2A) INHIBITOR? OR HBY(W) 793)

=> d l4 abs ibib kwic 1-14

L4 ANSWER 1 OF 14 DRUGU COPYRIGHT 2002 THOMSON DERWENT
AN 2000-01996 DRUGU M G
AB HIV-specific peptide antibody (Ab)-brefeldin A (BA) and Ab-glaucarubolone (GL) conjugates directed to cell surface viral glycoprotein epitopes were prepared. In-vitro using Crandall feline kidney (CFK), MOLT4 and human peripheral blood mononuclear cells (PBMC), Ab-BA and Ab-GL killed HIV-infected cells but not uninfected cells. The effectiveness of 1 Ab-BA conjugate (S-3) was increased by combination with zidovudine (**AZT**).
ABEX Succinylated BA (4) or GL (8) was conjugated to Ab which recognised surface epitopes of gp120 of HIV-1 (S-3, S-4 and S-5) and with Ab that recognised a major **FIV** envelope glycoprotein (S-I and S-II). **FIV**-infected CFK cells were killed by GL-S-II with EC50 1 uM; uninfected cells were not killed at 100 uM; BA-S-II killed infected, but not uninfected, cells at 1 uM. BA conjugated to S-3, S-4 or S-5 reduced growth of HIV infected MOLT4 cells by 35-65% after 65 hr without affecting uninfected cells; virus production by MOLT4 cells (p24 assay) was inhibited with IC50 1 nM. In PBMC, S-3, S-4 and S-5 conjugates killed 20-30% infected cells by 18 hr; S-3 was the most effective. S-3-BA 10 nM reduced PBMC p24 levels; Ab alone was ineffective; (8), BA or BA mixed with S-3 were cytotoxic to uninfected cells. In PBMC S-3-BA 10 nM + **AZT** 10 nM reduced virus production 90% in 9 days; 10 uM

AZT alone gave a similar effect. S-3-BA required 4-10 fold higher concentrations to affect viability than to reduce p24 production. S-3-BA + **AZT** was effective against both **AZT**-sensitive and **AZT**-resistant HIV strains. (YC)

ACCESSION NUMBER: 2000-01996 DRUGU M G
TITLE: Drug-antibody conjugates with anti-HIV activity.
AUTHOR: Paulik M; Grieco P; Kim C; Maxeiner H G; Grunert H P; Zeichhardt H; Morre D M; Morre D J
CORPORATE SOURCE: Univ.Purdue; Univ.Montana-State; Univ.Berlin-Free
LOCATION: West Lafayette, Ind.; Bozeman, Mont., USA; Berlin, Ger.
SOURCE: Biochem.Pharmacol. (58, No. 11, 1781-90, 1999) 9 Fig. 4 Tab. 37 Ref.
CODEN: BCPCA6 ISSN: 0006-2952
AVAIL. OF DOC.: Department of Medicinal Chemistry and Molecular Pharmacology, Purdue University, West Lafayette, IN 47907, U.S.A. (email: Morre@pharmacy.purdue.edu). (D.J.M.).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

AB. . . killed HIV-infected cells but not uninfected cells. The effectiveness of 1 Ab-BA conjugate (S-3) was increased by combination with zidovudine (**AZT**).

ABEX. . . Ab which recognised surface epitopes of gp120 of HIV-1 (S-3, S-4 and S-5) and with Ab that recognised a major **FIV** envelope glycoprotein (S-I and S-II). **FIV**-infected CFK cells were killed by GL-S-II with EC50 1 uM; uninfected cells were not killed at 100 uM; BA-S-II killed. . . was ineffective; (8), BA or BA mixed with S-3 were cytotoxic to uninfected cells. In PBMC S-3-BA 10 nM + **AZT** 10 nM reduced virus production 90% in 9 days; 10 uM **AZT** alone gave a similar effect. S-3-BA required 4-10 fold higher concentrations to affect viability than to reduce p24 production. S-3-BA + **AZT** was effective against both **AZT**-sensitive and **AZT** -resistant HIV strains. (YC)

CT [03] ZIDOVUDINE *PH; ZIDOVUDINE *DI; BREFELDIN-A *DI; BW-A-509U *RN; RESISTANCE *FT; VIRUCIDES *FT; REVERSE-TRANSCRIPTASE-INHIBITORS *FT; HIV-**PROTEASE-INHIBITORS** *FT; PEPTIDE-HYDROLASE-INHIBITORS *FT; PH *FT; DI *FT

L4 ANSWER 2 OF 14 DRUGU COPYRIGHT 2002 THOMSON DERWENT
AN 1997-28186 DRUGU M B
AB Reverse transcriptase (RT) associated RNA-ase H activity as a target for antiviral chemotherapy of HIV infections is reviewed. Highly purified recombinant RNA-ase H and model heteropolymer nucleic acid substrates allow evaluation of this activity, essential for retrovirus replication. HIV RNA-ase H inhibitors may include the marine sponge extract ilimaquinone, the ceftazidime degradation product HP 0.35, zidovudine (**AZT**) monophosphate, novemamines (novobiocin substructures) and nucleotide monomers and dimers. Allosteric inhibitors, which may bind in the vicinity of the RNA-ase H domain and change subdomain geometry, may be promising, providing methods to assess RNA-ase H function are available.
ABEX Despite drug-resistant viral variants, inhibitors of DNA synthesis are one of the most effective HIV infection and AIDS treatments via combination with DNA polymerase to prevent phosphodiester bond formation (nevirapine) or incorporation into nascent DNA to prevent synthesis (**AZT**, **3TC** and ddC). HIV RT DNA polymerase activity is assessed via partially purified recombinant enzymes but evaluation of

RNA-ase requires purified enzymes free from bacterial or cellular contamination.The isolated HIV-1 RT RNA-ase domain is compared with E. coli RNA-ase H and a revised catalytic mechanism for RNA-ase H mediated hydrolysis based on findings with mutants of the bacterial, HIV-1 and equine infectious anemia virus (EIAV). RNA-ase H-mediates DNA strand transfer, selection of (+)-strand primers and removal of (-)- and (+)-strand primers; since the gag-encoded nucleocapsid protein (NC) also has a role, antagonism may have therapeutic potential. Sulfated polyanions apparently antagonize RNA-ase H via antagonism of the surface glycoprotein gp120 with the CD4 receptor. Inhibition by ilimaquinone is probably via the p66 thumb subdomain via than the RNA7ase H domain (resistant to inhibition after Cys280 modification). HIV-1 RNA-ase H is inhibited by HP 0.35 (also **feline immunodeficiency virus**), **AZT** monophosphate and triphosphate, novemamines (comprising noviose and a substituted coumarines) and nucleotide monomers and dimers; allosteric inhibitors have promise. (E8/YC)

ACCESSION NUMBER: 1997-28186 DRUGU M B
TITLE: Reverse transcriptase-associated ribonuclease H activity as a target for antiviral chemotherapy.
AUTHOR: Rausch J W; Le Grice S F J
CORPORATE SOURCE: Univ.Case-Western-Reserve
LOCATION: Cleveland, Ohio, USA
SOURCE: Antiviral Chem.Chemother. (8, No. 3, 173-85, 1997) 5 Fig. 85 Ref. ISSN: 0956-3202
AVAIL. OF DOC.: Center for AIDS Research and Div. Infectious Diseases, Case Western Reserve University School of Med., 10900 Euclid Avenue, Cleveland, OH 44106-4984, U.S.A. (email: sfl:po.cwru.edu). (S.F.J.L.G.).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB. . . retrovirus replication. HIV RNA-ase H inhibitors may include the marine sponge extract ilimaquinone, the ceftazidime degradation product HP 0.35, zidovudine (**AZT**) monophosphate, novemamines (novobiocin substructures) and nucleotide monomers and dimers. Allosteric inhibitors, which may bind in the vicinity of the RNA-ase. . .
ABEX. . . treatments via combination with DNA polymerase to prevent phosphodiester bond formation (nevirapine) or incorporation into nascent DNA to prevent synthesis (**AZT**, **3TC** and ddC). HIV RT DNA polymerase activity is assessed via partially purified recombinant enzymes but evaluation of RNA-ase requires purified. . . than the RNA7ase H domain (resistant to inhibition after Cys280 modification). HIV-1 RNA-ase H is inhibited by HP 0.35 (also **feline immunodeficiency virus**), **AZT** monophosphate and triphosphate, novemamines (comprising noviose and a substituted coumarines) and nucleotide monomers and dimers; allosteric inhibitors have promise. (E8/YC)

L4 ANSWER 3 OF 14 DRUGU COPYRIGHT 2002 THOMSON DERWENT
AN 1997-14124 DRUGU B M
AB Mutations at the Met codon of the YMDD motif of reverse transcriptase (RT) in **feline immunodeficiency virus** (**FIV**) were responsible for resistance to (-)-beta-L-2',3'dideoxy -5-fluoro-3'thiacytidine ((-)-FTC) and (-)-beta-L-2',3'-dideoxy -3'-thiacytidine (**3TC**, lamivudine). Mutants were selected by culturing in (-)-FTC or produced by site-directed mutagenesis. Mutants showed low-level resistance to 2',3'-dideoxycytidine (ddC, zalcitabine,

Sigma-Chem.) and wild-type susceptibility to **AZT** (zidovudine, Glaxo-Wellcome), PMEA (Gilead-Sci.), ddI (didanosine), d4T (dideoxythymidinene-2+,3+, Bristol-Squibb) and PFA (phosphonoformate, foscarnet, Sigma-Chem.). When the Met-to-Val change in HIV-1 was introduced into wild-type **FIV**, the resulting virus was also **3TC**-resistant to the same degree as **FIV** Met-to-Thr mutant. **FIV** represents a model for evaluating **3TC** or (-)-FTC resistance.

ABEX (-)-FTC-resistant **FIV** mutants were selected and plaque purified. 2 Plaque purified mutants, designated FTR-2c and FTR-3c were 11- and 15-fold resistant to (-)-FTC. They were 6- to 8-fold resistant to **3TC** and additionally displayed low-level resistance to ddC. Both mutants showed wild-type susceptibility to **AZT**, PMEA, ddI, d4T and PFA. RT purified from FTR-2c was compared to wild-type **FIV** RT with respect to inhibition by ddCTP, (-)-FTCTP and AZTTP. RT from both FTR-2c and wild-type **FIV** were inhibited by (-)-FTCTP, 3TCTP and ddCTP in a manner that was competitive with respect to dCTP (Km values for dCTP were 7 uM for FTR-2C RT and 4.6 uM for wild-type **FIV** RT). The Ki value for the inhibition of FTR-2c RT by ddCTP was 12.5-fold greater than the Ki value for wild-type enzyme. Nucleotide analysis showed 2 point mutations in FTR-2c. One was a T-to-C transition at 2883 resulting in a Met-to Thr mutation. The second was an A-to-C transversion resulting in a change of Ile to Leu. To confirm the role of the mutation of Met-to-Thr, site directed mutagenesis was used to construct mutants which were 7- to 8-fold resistant to **3TC**. These results substantiate the role of the mutations at the Met codon of the YMDD motif in the resistance of **FIV** to (-)-FTC and **3TC**. (M59/KP)

ACCESSION NUMBER: 1997-14124 DRUGU B M
TITLE: A novel Met-to-Thr mutation in the YMDD motif of reverse transcriptase from **feline immunodeficiency virus** confers resistance to oxathiolane nucleosides.
AUTHOR: Smith R A; Remington K M; Lloyd R M Jr; Schinazi R Z; North T W
CORPORATE SOURCE: Univ.Montana-State; Univ.Emory
LOCATION: Missoula, Mont.; Decatur, Ga., USA
SOURCE: J.Virol. (71, No. 3, 2357-62, 1997) 3 Fig. 2 Tab. 59 Ref.
CODEN: JOVIAM ISSN: 0022-538X
AVAIL. OF DOC.: Division of Biological Sciences, University of Montana, Missoula, Montana 59812, U.S.A. (T.W.N.).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

TI A novel Met-to-Thr mutation in the YMDD motif of reverse transcriptase from **feline immunodeficiency virus** confers resistance to oxathiolane nucleosides.

AB Mutations at the Met codon of the YMDD motif of reverse transcriptase (RT) in **feline immunodeficiency virus** (**FIV**) were responsible for resistance to (-)-beta-L-2',3'dideoxy-5-fluoro-3'thiacytidine ((-)-FTC) and (-)-beta-L-2',3'-dideoxy-3'-thiacytidine (**3TC**, lamivudine). Mutants were selected by culturing in (-)-FTC or produced by site-directed mutagenesis. Mutants showed low-level resistance to 2',3'-dideoxycytidine (ddC, zalcitabine, Sigma-Chem.) and wild-type susceptibility to **AZT** (zidovudine, Glaxo-Wellcome), PMEA (Gilead-Sci.), ddI (didanosine), d4T (dideoxythymidinene-2+,3+, Bristol-Squibb) and PFA (phosphonoformate, foscarnet, Sigma-Chem.). When the Met-to-Val change in HIV-1 was

introduced into wild-type **FIV**, the resulting virus was also **3TC**-resistant to the same degree as **FIV** Met-to-Thr mutant. **FIV** represents a model for evaluating **3TC** or (-)-FTC resistance.

ABEX (-)-FTC-resistant **FIV** mutants were selected and plaque purified. 2 Plaque purified mutants, designated FTR-2c and FTR-3c were 11- and 15-fold resistant to (-)-FTC. They were 6- to 8-fold resistant to **3TC** and additionally displayed low-level resistance to ddC. Both mutants showed wild-type susceptibility to **AZT**, PMEA, ddI, d4T and PFA. RT purified from FTR-2c was compared to wild-type **FIV** RT with respect to inhibition by ddCTP, (-)-FTCTP and AZTTP. RT from both FTR-2c and wild-type **FIV** were inhibited by (-)-FTCTP, 3TCTP and ddCTP in a manner that was competitive with respect to dCTP (Km values for dCTP were 7 uM for FTR-2C RT and 4.6 uM for wild-type **FIV** RT). The Ki value for the inhibition of FTR-2c RT by ddCTP was 12.5-fold greater than the Ki value for. . . of the mutation of Met-to-Thr, site directed mutagenesis was used to construct mutants which were 7- to 8-fold resistant to **3TC**. These results substantiate the role of the mutations at the Met codon of the YMDD motif in the resistance of **FIV** to (-)-FTC and **3TC** . (M59/KP)

CT. . . STAVUDINE *RC; FOSCARNET *RC; IN-VITRO *FT; DRUG-COMPARISON *FT; VIRUCIDE *FT; MODE-OF-ACT. *FT; MUTATION *FT; CODON *FT; EC-2.7.7.49 *FT; REVERSE-TRANSCRIPTASE-INHIBITOR *FT; **FIV**-VIRUS *FT; RESISTANCE *FT; GENETICS *FT; DNA-NUCLEOTIDYLTRANSFERASE *FT; LEUKOVIRUS *FT; VIRUS *FT

CT. . . STAVUDINE *RC; FOSCARNET *RC; IN-VITRO *FT; DRUG-COMPARISON *FT; VIRUCIDE *FT; MODE-OF-ACT. *FT; MUTATION *FT; CODON *FT; EC-2.7.7.49 *FT; REVERSE-TRANSCRIPTASE-INHIBITOR *FT; **FIV**-VIRUS *FT; RESISTANCE *FT; GENETICS *FT; DNA-NUCLEOTIDYLTRANSFERASE *FT; LEUKOVIRUS *FT; VIRUS *FT

L4 ANSWER 4 OF 14 DRUGU COPYRIGHT 2002 THOMSON DERWENT

AN 1994-51383 DRUGU M

AB The in-vitro activity of dideoxycytidine (ddC; zalcitabine), ddI (didanosine), ddA (dideoxyadenosine-2+,3+), **AZT** (zidovudine), DMSO, pepstatin A (PA) and Na fusidate (NF, all Sigma-Chem.), 2',3'-didehydro-2',3'- dideoxythymidine (d4T), lamivudine (**3TC**) and TIBO (all Glaxo) and aurintricarboxylic acid (AA), ribavirin (RV), ddU (dideoxyuridine-2+,3+), phosphonoformic acid (PA, foscarnet), taurolithocholic acid (TCA), Roche **protease inhibitor** (RPI), papaverine (PV), butyldeoxynojirimycin (BuDNJ) and gossypol (GP) against 2 **feline immunodeficiency virus** (**FIV**) strains was determined in Crandell-Reese feline kidney (CRFK) cells or primary feline lymphocytes (FL). The nucleoside-analog reverse transcriptase inhibitors were the most potent inhibitors of p24 antigen production. The only other active agents were AA, PA and BuDNJ.

ABEX Strains **FIV**-E77 and **FIV**-8 were grown in FL and CRFK cells, respectively. **AZT**, ddC, ddI, d4T, ddA and **3TC** IC50 ranged from 0.05-0.2, 0.07-0.15, 0.23-0.87, 2.0-2.6, 1.8-1.9 and 0.04-0.09 mg/l, respectively; ddU did not inhibit FLU p24 antigen production by FL or CRFX cells. High ddI, ddA and **3TC** concentrations were cytotoxic to both cell-lines (CT50, 410-500, 250-420 and 250-480 mg/l, respectively). DMSO (in which the test agents were dissolved) had no antiviral activity but was cytotoxic to FL (CT50, 2600 mg/l) and CRFK cells (4900 mg/l) at 1 g/l. The IC50 of the other agents were: AA, 17 mg/l; PA, 5.8 mg/l; TIBO, RV and PA, over 50 mg/l; RPI, 12-31 mg/l; GP, 2.6 mg/l; TCA, 37 mg/l; PV, 9.6 mg/l; NF, 18 mg/l; and

BuDNJ, 7.4-over 25 mg/l. (W132/SDB)
ACCESSION NUMBER: 1994-51383 DRUGU M
TITLE: Susceptibility in cell culture of **feline immunodeficiency virus** to eighteen antiviral agents.
AUTHOR: Smyth N R; McCracken C; Gaskell R M; Cameron J M; Coates J A V; Gaskell C J
CORPORATE SOURCE: Univ.Liverpool; Glaxo
LOCATION: Liverpool, Greenford, United Kingdom
SOURCE: J.Antimicrob.Chemother. (34, No. 4, 589-94, 1994) 1 Tab. 11 Ref.
CODEN: JACHDX ISSN: 0305-7453
AVAIL. OF DOC.: Department of Veterinary Clinical Science and Animal Husbandry, University of Liverpool, Leahurst, Neston, South Wirral L64 7TE, England. (Bennett M; 8 authors).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

TI Susceptibility in cell culture of **feline immunodeficiency virus** to eighteen antiviral agents.

AB The in-vitro activity of dideoxycytidine (ddC; zalcitabine), ddI (didanosine), ddA (dideoxyadenosine-2+,3+), **AZT** (zidovudine), DMSO, pepstatin A (PA) and Na fusidate (NF, all Sigma-Chem.), 2',3'-didehydro-2',3'- dideoxythymidine (d4T), lamivudine (**3TC**) and TIBO (all Glaxo) and aurintricarboxylic acid (AA), ribavirin (RV), ddU (dideoxyuridine-2+,3+), phosphonoformic acid (PA, foscarnet), taurolithocholic acid (TCA), Roche **protease inhibitor** (RPI), papaverine (PV), butyldeoxynojirimycin (BuDNJ) and gossypol (GP) against 2 **feline immunodeficiency virus** (**FIV**) strains was determined in Crandell-Reese feline kidney (CRFK) cells or primary feline lymphocytes (FL). The nucleoside-analog reverse transcriptase inhibitors were. . .

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CT IN-VITRO *FT; **FIV**-VIRUS *FT; VIRUCIDE *FT; CRFK-CELL *FT; KIDNEY *FT; TISSUE-CULTURE *FT; CAT *FT; LYMPHOCYTE *FT; LEUKOVIRUS *FT; VIRUS *FT; LAB.ANIMAL *FT

CT IN-VITRO *FT; **FIV**-VIRUS *FT; VIRUCIDE *FT; CRFK-CELL *FT; KIDNEY *FT; TISSUE-CULTURE *FT; CAT *FT; LYMPHOCYTE *FT; LEUKOVIRUS *FT; VIRUS *FT; LAB.ANIMAL *FT

L4 ANSWER 5 OF 14 DRUGU COPYRIGHT 2002 THOMSON DERWENT
AN 1993-35108 DRUGU T M
AB The molecular biology and clinical implications of the resistance of HIV to zidovudine (**AZT**) and the other nucleoside and nonnucleoside inhibitors of retroviral reverse transcriptase (ddI (didanosine) and ddC) are reviewed. Selection for resistance to highly promising nonnucleoside inhibitors of reverse transcriptase (RTase) was demonstrated in-vitro before extended clinical use of the drugs. It is assumed that in order to combat the resistance of HIV to antiretroviral drugs and for chemotherapy to be effective, regimens that combine several agents will

have to be used.

ABEX In subjects not treated with **AZT**, the range of susceptibility was narrow. After 6 mth of **AZT** therapy, almost all isolates showed some reduction in susceptibility. Isolates resistant to **AZT** were cross-resistant to 3-azido-2,3-dideoxyuridine (AZdU, CS-87), 3-azido-2,3-dideoxy guanosine and 3-azido-2,3-dideoxy adenosine, but not to ddC or foscarnet. 2/11 **AZT** resistant HIV isolates were cross-resistant to didehydrodideoxythymidine. **AZT** resistance was observed sooner in isolates from patients with late stage HIV-infection, than in those with early-stage disease. Resistance was more likely to emerge in patients with low CD4 lymphocyte counts and in those given higher **AZT** doses. Cumulative mutations contributed either additively or synergistically to stepwise reductions in susceptibility. Isolates that were resistant to **AZT** when ddI therapy began increased their susceptibility to **AZT** as their susceptibility to ddI decreased. Similar results were seen for ddC. Pyridinone inhibitors selected for mutants with reduced susceptibility. Phase I and II trials have confirmed the rapid selection of L-697661 and nevirapine for resistant virus in-vivo. The in-vitro selection of a mutant that confers resistance to a **protease inhibitor** that resulted in an 8-fold reduction in susceptibility was observed. The loss of antiviral and CD4 cell activities was associated with the emergence of resistance during administration of L-697661 and nevirapine. Resistant mutants of **feline immunodeficiency virus (FIV)** have been readily selected and, like resistant isolates of HIV, resistant **FIV** isolates are cross-resistant to other similar compounds. (W91/ECB)

ACCESSION NUMBER: 1993-35108 DRUGU T M
TITLE: Resistance of Clinical Isolates of Human Immunodeficiency Virus to Antiretroviral Agents.
AUTHOR: Richman D D
LOCATION: Louisiana, Jolla, California, United States
SOURCE: Antimicrob.Agents Chemother. (37, No. 6, 1207-13, 1993) 1 Fig. 2 Tab. 60 Ref.
CODEN: AMACCQ ISSN: 0066-4804
AVAIL. OF DOC.: Departments of Pathology and Medicine, 0679, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093-0679, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

AB The molecular biology and clinical implications of the resistance of HIV to zidovudine (**AZT**) and the other nucleoside and nonnucleoside inhibitors of retroviral reverse transcriptase (ddI (didanosine) and ddC) are reviewed. Selection for resistance. . .

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mutations contributed either additively or synergistically to stepwise reductions in susceptibility. Isolates that were resistant to **AZT** when ddI therapy began increased their susceptibility to **AZT** as their susceptibility to ddI decreased. Similar results were seen for ddC. Pyridinone inhibitors selected for mutants with reduced susceptibility.. . . selection of L-697661 and nevirapine for resistant virus in-vivo. The in-vitro selection of a mutant that confers resistance to a **protease inhibitor** that resulted in an 8-fold reduction in susceptibility was observed. The loss of antiviral and CD4 cell activities was associated with the emergence of resistance during administration of L-697661 and nevirapine. Resistant mutants of **feline immunodeficiency virus** (**FIV**) have been readily selected and, like resistant isolates of HIV, resistant **FIV** isolates are cross-resistant to other similar compounds. (W91/ECB)

CT . . . ZIDOVUDINE *TR; DIDANOSINE *TR; DIDEOXYCYTIDINE-2+,3+ *TR; CS-87 *TR; AZIDODIDEOXYGUANOSINE-2+,3+ *TR; FOSCARNET *TR; AZIDODIDEOXYADENOSINE-2+,3+ *TR; L-697661 *TR; NEVIRAPINE *TR; HELPER-CELL *FT; **FIV**-VIRUS *FT; LYMPHOCYTE *FT; THYMOCYTE *FT; PH *FT; TR *FT

L4 ANSWER 6 OF 14 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AB In vitro and in vivo prophylactic and therapeutic efficacy of **AZT** **/3TC** treatment was evaluated against **feline immunodeficiency virus** (**FIV**) infection. In vitro studies utilized **FIV**-infected peripheral blood mononuclear cells (PBMCs) or **FIV**-infected T-cell lines treated with **AZT** (**azidothymidine**) alone, **3TC** alone, or **AZT/3TC** combination and tested for anti-**FIV** activity and drug toxicity. **AZT/3TC** combination had additive to synergistic anti-**FIV** activities in primary PBMC but not in chronically infected cell lines. In vivo studies consisted of four treatment groups (n=15) of SPF cats receiving **AZT/3TC** combination (5-75mg/kg/drug PO BID for 8 or 11 weeks) and one control group (n=9) receiving oral placebo. Group I (n=6, 150mg/kg/drug/day) was treated starting 3 days pre-**FIV** inoculation, whereas Group II (n=3, 150mg/kg/drug/day) and Group III (n=3, 100mg/kg/drug/day) treatments were simultaneous with **FIV** inoculation. Group IV treatment (n=3, 100mg/kg/drug/day) was initiated 2 weeks post-**FIV** inoculation. All cats were monitored for drug toxicity and **FIV** infection. Eighty-three percent of cats in Group I and 33% of cats in Groups II and III were completely protected from **FIV** infection. A significant delay in infection and antibody seroconversion was observed in all unprotected cats from Groups I, II and III. Group IV cats had only a slight delay in **FIV** antibody seroconversion. Adverse drug reactions (anemia and neutropenia) were observed at high doses (100-150mg/kg/drug/day) were reversible upon lowering the dose (20mg/kg/drug/day). In contrast, **AZT/3TC** treatment had no anti-**FIV** activity in chronically infected cats. Furthermore, severe clinical symptoms caused by adverse drug reactions were observed in some of these cats. Overall, **AZT/3TC** treatment is effective for prophylaxis but not for therapeutic use in chronically **FIV**-infected cats.

ACCESSION NUMBER: 2002127530 EMBASE

TITLE: Is **AZT/3TC** therapy effective against **FIV** infection or immunopathogenesis?.

AUTHOR: Arai M.; Earl D.D.; Yamamoto J.K.

09/763,037

CORPORATE SOURCE: J.K. Yamamoto, Department of Pathobiology, College of Veterinary Medicine, University of Florida, P.O. Box 110880, Gainesville, FL 32611-0880, United States. yamamotoj@mail.vetmed.ufl.edu
SOURCE: Veterinary Immunology and Immunopathology, (2002) 85/3-4 (189-204).
Refs: 67
ISSN: 0165-2427 CODEN: VIIMDS
PUBLISHER IDENT.: S 0165-2427(01)00426-3
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

TI Is **AZT/3TC** therapy effective against **FIV** infection or immunopathogenesis?.

AB In vitro and in vivo prophylactic and therapeutic efficacy of **AZT/3TC** treatment was evaluated against **feline immunodeficiency virus** (**FIV**) infection. In vitro studies utilized **FIV**-infected peripheral blood mononuclear cells (PBMCs) or **FIV**-infected T-cell lines treated with **AZT** (**azidothymidine**) alone, **3TC** alone, or **AZT/3TC** combination and tested for anti-**FIV** activity and drug toxicity. **AZT/3TC** combination had additive to synergistic anti-**FIV** activities in primary PBMC but not in chronically infected cell lines. In vivo studies consisted of four treatment groups (n=15) of SPF cats receiving **AZT/3TC** combination (5-75mg/kg/drug PO BID for 8 or 11 weeks) and one control group (n=9) receiving oral placebo. Group I (n=6, 150mg/kg/drug/day) was treated starting 3 days pre-**FIV** inoculation, whereas Group II (n=3, 150mg/kg/drug/day) and Group III (n=3, 100mg/kg/drug/day) treatments were simultaneous with **FIV** inoculation. Group IV treatment (n=3, 100mg/kg/drug/day) was initiated 2 weeks post-**FIV** inoculation. All cats were monitored for drug toxicity and **FIV** infection. Eighty-three percent of cats in Group I and 33% of cats in Groups II and III were completely protected from **FIV** infection. A significant delay in infection and antibody seroconversion was observed in all unprotected cats from Groups I, II and III. Group IV cats had only a slight delay in **FIV** antibody seroconversion. Adverse drug reactions (anemia and neutropenia) were observed at high doses (100-150mg/kg/drug/day) were reversible upon lowering the dose (20mg/kg/drug/day). In contrast, **AZT/3TC** treatment had no anti-**FIV** activity in chronically infected cats. Furthermore, severe clinical symptoms caused by adverse drug reactions were observed in some of these cats. Overall, **AZT/3TC** treatment is effective for prophylaxis but not for therapeutic use in chronically **FIV**-infected cats. .COPYRGT. 2002 Elsevier Science B.V. All rights reserved.

CT Medical Descriptors:
***Feline immunodeficiency virus**
*virus infection: DT, drug therapy
immunopathogenesis
drug efficacy
mononuclear cell
T lymphocyte

antiviral activity
cell line
inoculation
dose response
dose time effect relation
seroconversion
infection rate
anemia
neutropenia
prophylaxis
nonhuman
controlled study
animal cell
article
*zidovudine: CB,. . .

L4 ANSWER 7 OF 14 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AB In view of close similarities at the molecular and clinical levels, **feline immunodeficiency virus** (**FIV**) infection of the domestic cat is subject of increasing attention as an animal model for human immunodeficiency virus (HIV) infection. A range of reverse transcriptase inhibitors effective against HIV are also active against **FIV**, allowing successful use of the cat model to investigate drug interactions and resistance development. Nevertheless, while combined nucleoside analog and **protease inhibitor** usage has proven remarkably effective in treating HIV infection, combination antiretroviral therapy of **FIV** infection has been hampered by lack of **protease inhibitors** specific for **FIV**. In an attempt to circumvent this problem, we have examined the feasibility of applying in the **FIV** system combination protocols lacking a **protease inhibitor**. We now report that, as observed during HIV infection, the nucleoside analog abacavir (ABC or 1592U89) is able to effectively block in vitro **FIV** -replication. Furthermore, we demonstrate that combined usage of ABC with the nucleoside analogs zidovudine (ZDV or **AZT**) and lamivudine (**3TC**) also blocks in vitro **FIV** replication in a synergistic manner. However, in contrast to its effect on HIV replication, the ribonucleotide reductase inhibitor hydroxyurea (HU) is unable to effectively control in vitro **FIV** replication.

ACCESSION NUMBER: 2001380014 EMBASE
TITLE: Combined effect of zidovudine (ZDV), lamivudine (**3TC**) and abacavir (ABC) antiretroviral therapy in suppressing in vitro **FIV** replication.
AUTHOR: Bisset L.R.; Lutz H.; Boni J.; Hofmann-Lehmann R.; Luthy R.; Schupbach J.
CORPORATE SOURCE: J. Schupbach, Swiss Natl. Center for Retroviruses, University of Zurich, Gloriastrasse 30, CH-8028 Zurich, Switzerland. jschupb@immv.unizh.ch
SOURCE: Antiviral Research, (2002) 53/1 (35-45).
Refs: 43
ISSN: 0166-3542 CODEN: ARSRDR
PUBLISHER IDENT.: S 0166-3542(01)00190-5
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
030 Pharmacology
037 Drug Literature Index

LANGUAGE: English
SUMMARY LANGUAGE: English
TI Combined effect of zidovudine (ZDV), lamivudine (**3TC**) and abacavir (ABC) antiretroviral therapy in suppressing in vitro **FIV** replication.
AB In view of close similarities at the molecular and clinical levels, **feline immunodeficiency virus** (**FIV**) infection of the domestic cat is subject of increasing attention as an animal model for human immunodeficiency virus (HIV) infection. A range of reverse transcriptase inhibitors effective against HIV are also active against **FIV**, allowing successful use of the cat model to investigate drug interactions and resistance development. Nevertheless, while combined nucleoside analog and **protease inhibitor** usage has proven remarkably effective in treating HIV infection, combination antiretroviral therapy of **FIV** infection has been hampered by lack of **protease inhibitors** specific for **FIV**. In an attempt to circumvent this problem, we have examined the feasibility of applying in the **FIV** system combination protocols lacking a **protease inhibitor**. We now report that, as observed during HIV infection, the nucleoside analog abacavir (ABC or 1592U89) is able to effectively block in vitro **FIV** -replication. Furthermore, we demonstrate that combined usage of ABC with the nucleoside analogs zidovudine (ZDV or **AZT**) and lamivudine (**3TC**) also blocks in vitro **FIV** replication in a synergistic manner. However, in contrast to its effect on HIV replication, the ribonucleotide reductase inhibitor hydroxyurea (HU) is unable to effectively control in vitro **FIV** replication.
CT Medical Descriptors:
***Feline immunodeficiency virus**
*virus replication
*virus infection: DT, drug therapy
*virus inhibition
in vitro study
feasibility study
Human immunodeficiency virus infection
drug potentiation
drug effect
nonhuman
animal model
controlled study
animal cell
article
priority journal

L4 ANSWER 8 OF 14 EMBASE
AB Mutants of **feline immunodeficiency virus** (**FIV**) resistant to (-)-.beta.- 2',3'-dideoxy-3'-thiacytidine (**3TC**) were selected by culturing virus in the presence of increasing stepwise concentrations of **3TC**. Two plaque-purified variants were isolated from the original mutant population, and both of these mutants were resistant to **3TC**. Surprisingly, these mutants were also phenotypically resistant to 3'-azido-3'-deoxythymidine (**AZT**) and to the combination of **3TC** and **AZT**. Purified reverse transcriptase (RT) from one of these plaque-purified mutants was resistant to the 5'-triphosphates of **3TC** and **AZT**. DNA sequence analysis of the RT-encoding region of the pol gene amplified from the plaque-purified mutants revealed a Pro-to-Ser

mutation at position 156 of RT. A site-directed mutant of FTV engineered to contain this Pro-156-Ser mutation was resistant to **3TC**, **AZT**, and the combination of **3TC** and **AZT**, confirming the role of the Pro-156-Ser mutation in the resistance of **FIV** to these two nucleoside analogs. This represents the first report of a lentiviral mutant resistant to the combination of **AZT** and **3TC** due to a single, unique point mutation.

ACCESSION NUMBER: 1998071136 EMBASE
TITLE: A novel point mutation at position 156 of reverse transcriptase from **feline immunodeficiency virus** confers resistance to the combination of (-)- .beta.-2',3'-dideoxy-3'-thiacytidine and 3'-azido-3'-deoxythymidine.
AUTHOR: Smith R.A.; Remington K.M.; Preston B.D.; Schinazi R.F.; North T.W.
CORPORATE SOURCE: T.W. North, Center for Comparative Medicine, University of California, Davis, CA 95616, United States. twnorth@ucdavis.edu
SOURCE: Journal of Virology, (1998) 72/3 (2335-2340). Refs: 62
ISSN: 0022-538X CODEN: JOVIAM
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

TI A novel point mutation at position 156 of reverse transcriptase from **feline immunodeficiency virus** confers resistance to the combination of (-)- .beta.-2',3'-dideoxy-3'-thiacytidine and 3'-azido-3'-deoxythymidine.

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CT Medical Descriptors:
*immune deficiency: DR, drug resistance
*immune deficiency: ET, etiology
***feline immunodeficiency virus**
point mutation
drug resistance
sequence analysis
amino acid substitution

nonhuman
article
priority journal
*rna directed dna polymerase
*lamivudine: CB, drug combination
*zidovudine: CB, drug combination

L4 ANSWER 9 OF 14 LIFESCI COPYRIGHT 2002 CSA

AB Progression to AIDS in human immunodeficiency virus type 1 (HIV-1)-positive individuals is characterized by a slow destruction of the immune system and a depletion of CD4 super(+) cells in the peripheral blood. The complex mechanism of CD4 super(+) cell disappearance is poorly understood, but this depletion may be attributable in part to a superantigen effect, apoptosis, viral cytopathicity, or combinations of all of these. A rough correlation exists between increases in viral load in lymphoid organs, rate of disease progression, and extent of CD4 super(+) cell depletion. Anti-HIV chemotherapy with agents such as 3'-azido-3'-deoxythymidine (**AZT**) has resulted in at least transient decreases in viral load and increases in CD4 super(+) cells. The anti-HIV drugs currently employed in clinical trials or licensed for AIDS therapy generally fall into three major categories, i.e., nucleoside analogs, nonnucleoside reverse transcriptase (RT) inhibitors, and HIV proteinase inhibitors. This review focuses on the inhibition of HIV-1 RT and reverse transcription by nucleoside analogs and on mechanisms of resistance to nucleoside analogs. **AZT** possesses activity against a number of retroviruses besides HIV-1. **AZT** blocks HIV-1 replication at low concentrations; i.e., the effective concentration for 50% percent inhibition (IC sub(50)) is approximately 0.01 mu M. In addition, this drug is largely nontoxic for T lymphocytes; i.e., the cell culture inhibitory dose for 50% inhibition of cell growth (CCID sub(50)) is approximately 10 to 50 mu M. The active form of **AZT**, i.e., **AZT** 5'-triphosphate (**AZT**-TP), phosphorylated by cellular nucleoside kinases, is thought to inhibit HIV-1 reverse transcription both as a competitive inhibitor of RT and as a chain terminator of DNA elongation. When studied in phase I and phase II clinical trials, **AZT** treatment resulted in increased numbers of CD4 super(+) cells, decreased occurrences of opportunistic infections, and decreased viral loads. Many of the initially serious toxic effects of **AZT**, e.g., bone marrow suppression and anemia, have been alleviated by lowering the dosage and by administering recombinant erythropoietin. **AZT** can cross the blood-brain barrier and may reverse certain neurological abnormalities such as AIDS dementia. However, **AZT** treatment for prolonged periods also resulted in the emergence of drug-resistant viral isolates that displayed normal replication kinetics and up to 100-fold resistance to this drug. In addition, a direct correlation between the development of **AZT** resistance and clinical progression to AIDS and death has been established. A number of other dideoxynucleoside triphosphates (ddNTP), analogous to native deoxynucleoside triphosphates (dNTP) but deficient in their 3' hydroxyl group, have also been shown to inhibit HIV replication in CD4 super(+) cells. Relatively few of these compounds, e.g., 2',3'-dideoxyinosine (ddI or didanosine) and 2',3'-dideoxycytidine (ddC or zalcitabine), have IC sub(50)s of below 10 mu M. Derivatives of these analogs, such as the racemic mixture of 2',3'-dideoxy-3'-thiacytidine (BCH-189) and its negative enantiomer (**3TC** or lamivudine), 2',3'-dideoxy-5'-fluoro-3'-thiacytidine, 3'-fluoro-3'-deoxythymidine (FLT), carbocyclic-2',3'-didehydro-2',3'-dideoxyguanosine (carbovir), 3'-azido-2',3'-dideoxyuridine, and 2',3'-didehydro-2',3'-dideoxythymidine (d4T), also inhibited HIV

infections of CD4 super(+) cells and in many cases showed less cytotoxicity and had lower CCID sub(50)s than **AZT**. These ddNTPs have all entered all clinical trials, although resistance continues to be a problem. The mechanisms of antiviral action by nucleoside analogs in tissue culture are not fully understood. Nucleoside analog triphosphates may block acute infection by HIV and other retroviruses through inhibition of RT and chain termination. However, **AZT** has also been reported to block virus replication in chronically infected cells, to interfere with virus maturation, and to disrupt syncytium formation. However, **AZT** did not block cell-to-cell HIV transmission. In the related **feline immunodeficiency virus** model, selection of resistance to **AZT** resulted in mutations outside the RT-coding region, suggesting that viral proteins besides RT may also play a role in resistance. Breakthrough HIV replication in CD4 super(+) cells was observed despite constant exposure to high **AZT** concentrations. Certain nonnucleoside inhibitors of RT, i.e., phosphonoformate and Nevirapine, and other nucleoside analogs, i.e., carbovir, ddI, FLT, and ddC, may act synergistically with **AZT** to delay HIV-1 replication in tissue culture.

ACCESSION NUMBER: 96:73713 LIFESCI
TITLE: Mechanisms of nucleoside analog antiviral activity and resistance during human immunodeficiency virus reverse transcription
AUTHOR: Arts, E.J.; Wainberg, M.A.
CORPORATE SOURCE: Lady Davis Inst.-Jewish General Hosp., 3755 Cote-Ste-Catherine Rd., Montreal, Canada H3T 1E2
SOURCE: ANTIMICROB. AGENTS CHEMOTHER., (1996) vol. 40, no. 3, pp. 527-540.
ISSN: 0066-4804.
DOCUMENT TYPE: Journal
TREATMENT CODE: General Review
FILE SEGMENT: V; A; N
LANGUAGE: English

AB . . . lymphoid organs, rate of disease progression, and extent of CD4 super(+) cell depletion. Anti-HIV chemotherapy with agents such as 3'-azido-3'-deoxythymidine (**AZT**) has resulted in at least transient decreases in viral load and increases in CD4 super(+) cells. The anti-HIV drugs currently. . . on the inhibition of HIV-1 RT and reverse transcription by nucleoside analogs and on mechanisms of resistance to nucleoside analogs. **AZT** possesses activity against a number of retroviruses besides HIV-1. **AZT** blocks HIV-1 replication at low concentrations; i.e., the effective concentration for 50% percent inhibition (IC sub(50)) is approximately 0.01 mu. . . dose for 50% inhibition of cell growth (CCID sub(50)) is approximately 10 to 50 mu M. The active form of **AZT**, i.e., **AZT** 5'-triphosphate (**AZT**-TP), phosphorylated by cellular nucleoside kinases, is thought to inhibit HIV-1 reverse transcription both as a competitive inhibitor of RT and as a chain terminator of DNA elongation. When studied in phase I and phase II clinical trials, **AZT** treatment resulted in increased numbers of CD4 super(+) cells, decreased occurrences of opportunistic infections, and decreased viral loads. Many of the initially serious toxic effects of **AZT**, e.g., bone marrow suppression and anemia, have been alleviated by lowering the dosage and by administering recombinant erythropoietin. **AZT** can cross the blood-brain barrier and may reverse certain neurological abnormalities such as AIDS dementia. However, **AZT** treatment for prolonged periods also resulted in the emergence of drug-resistant viral isolates that displayed normal replication kinetics and up to 100-fold resistance to this drug. In

addition, a direct correlation between the development of **AZT** resistance and clinical progression to AIDS and death has been established. A number of other dideoxynucleoside triphosphates (ddNTP), analogous to. . . below 10 mu M. Derivatives of these analogs, such as the racemic mixture of 2',3'-dideoxy-3'-thiacytidine (BCH-189) and its negative enantiomer (**3TC** or lamivudine), 2',3'-dideoxy-5'-fluoro-3'-thiacytidine, 3'-fluoro-3'-deoxythymidine (FLT), carbocyclic-2',3'-didehydro-2',3'-dideoxyguanosine (carbovir), 3'-azido-2',3'-dideoxyuridine, and 2',3'-didehydro-2',3'-dideoxythymidine (d4T), also inhibited HIV infections of CD4 super(+) cells and in many cases showed less cytotoxicity and had lower CCID sub(50)s than **AZT**. These ddNTPs have all entered all clinical trials, although resistance continues to be a problem. The mechanisms of antiviral action. . . Nucleoside analog triphosphates may block acute infection by HIV and other retroviruses through inhibition of RT and chain termination. However, **AZT** has also been reported to block virus replication in chronically infected cells, to interfere with virus maturation, and to disrupt syncytium formation. However, **AZT** did not block cell-to-cell HIV transmission. In the related **feline immunodeficiency virus** model, selection of resistance to **AZT** resulted in mutations outside the RT-coding region, suggesting that viral proteins besides RT may also play a role in resistance. Breakthrough HIV replication in CD4 super(+) cells was observed despite constant exposure to high **AZT** concentrations. Certain nonnucleoside inhibitors of RT, i.e., phosphonoformate and Nevirapine, and other nucleoside analogs, i.e., carbovir, ddI, FLT, and ddC, may act synergistically with **AZT** to delay HIV-1 replication in tissue culture.

L4 ANSWER 10 OF 14 CAPLUS COPYRIGHT 2002 ACS

AB The subject invention pertains to materials and methods for detecting, preventing and treating retroviral infections in humans and other animals susceptible to infection by retrovirus. It has been discovered that **feline immunodeficiency virus** (**FIV**) can be transmitted from cats to humans and that the **FIV** can infect human cells in vivo and that antibodies generated by the infected person cross-react with HIV antigens. Thus, the methods and compns. of the subject invention can be used to detect, prevent and treat **FIV** infection in humans and other non-feline animals that are susceptible to **FIV** infection. The methods and compns. of the invention can also be used to prevent and treat infection by HIV in humans. For example, vaccine compn. comprise **FIV** proteins and peptides, recombinant viral vector-based **FIV** constructs, attenuated or inactivated **FIV** viral isolates, and the like, having antigenic or immunogenic properties.

ACCESSION NUMBER: 2002:675873 CAPLUS
DOCUMENT NUMBER: 137:206521
TITLE: Materials and methods for detecting, preventing, and treating retroviral infection
INVENTOR(S): Yamamoto, Janet K.; Janelle, Jennifer White; Torres, Barbara Aurea; Arai, Maki; Tanabe, Taishi; Pu, Ruiyu
PATENT ASSIGNEE(S): University of Florida, USA
SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002067984	A2	20020906	WO 2002-US5181	20020222

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-270745P P 20010222

AB The subject invention pertains to materials and methods for detecting, preventing and treating retroviral infections in humans and other animals susceptible to infection by retrovirus. It has been discovered that **feline immunodeficiency virus** (**FIV**) can be transmitted from cats to humans and that the **FIV** can infect human cells in vivo and that antibodies generated by the infected person cross-react with HIV antigens. Thus, the methods and compns. of the subject invention can be used to detect, prevent and treat **FIV** infection in humans and other non-feline animals that are susceptible to **FIV** infection. The methods and compns. of the invention can also be used to prevent and treat infection by HIV in humans. For example, vaccine compn. comprise **FIV** proteins and peptides, recombinant viral vector-based **FIV** constructs, attenuated or inactivated **FIV** viral isolates, and the like, having antigenic or immunogenic properties.

ST **feline immunodeficiency virus** antigen vaccine retroviral infection; HIV1 infection **FIV** antigen cross reactivity; antibody **FIV** antigen detection retroviral infection

IT Envelope proteins
Proteins
gag proteins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**FIV** and HIV; detection, prevention, and treatment of retroviral infections)

IT Animal cell
(**FIV**-infected, inactivated; detection, prevention, and treatment of retroviral infections)

IT Peptides, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**FIV**; detection, prevention, and treatment of retroviral infections)

IT Cat (Felis catus)
(HIV-1 antigen reactivity with **FIV**-infected and **FIV** -vaccinated cat serum)

IT Antibodies
RL: ANT (Analyte); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study)
(against **FIV**, cross-reactivity with HIV- antigens; detection, prevention, and treatment of retroviral infections)

IT Polynucleotides
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(encoding **FIV** and HIV proteins; detection, prevention, and treatment of retroviral infections)

IT DNA formation factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene 41; HIV-1 antigen reactivity with **FIV**-infected and **FIV**-vaccinated cat serum)
IT Envelope proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gp120env; HIV-1 antigen reactivity with **FIV**-infected and **FIV**-vaccinated cat serum)
IT Envelope proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gp160env; HIV-1 antigen reactivity with **FIV**-infected and **FIV**-vaccinated cat serum)
IT Antibodies
RL: ANT (Analyte); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study)
(humanized, monoclonal, against **FIV**, cross-reactivity with HIV- antigens; detection, prevention, and treatment of retroviral infections)
IT Antibodies
RL: ANT (Analyte); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study)
(monoclonal, humanized, against **FIV**, cross-reactivity with HIV- antigens; detection, prevention, and treatment of retroviral infections)
IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p18; HIV-1 antigen reactivity with **FIV**-infected and **FIV**-vaccinated cat serum)
IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p24; HIV-1 antigen reactivity with **FIV**-infected and **FIV**-vaccinated cat serum)
IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p32; HIV-1 antigen reactivity with **FIV**-infected and **FIV**-vaccinated cat serum)
IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p51; HIV-1 antigen reactivity with **FIV**-infected and **FIV**-vaccinated cat serum)
IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p55; HIV-1 antigen reactivity with **FIV**-infected and **FIV**-vaccinated cat serum)
IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p66; HIV-1 antigen reactivity with **FIV**-infected and **FIV**-vaccinated cat serum)
IT **Feline immunodeficiency virus**
(subtypes A, B and D; detection, prevention, and treatment of retroviral infections)
IT 30516-87-1, **Azidothymidine** 134678-17-4, Lamivudine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination with; detection, prevention, and treatment of retroviral infections)
IT 9068-38-6, Reverse transcriptase 144114-21-6, HIV **protease**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors**, combination with; detection, prevention, and

treatment of retroviral infections)

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AB Objective-To compare in vitro replication kinetics and nucleoside analog susceptibilities of a natural **feline immunodeficiency virus** (**FIV**) isolate (**FIV**-Maxam), a mol. clone of **FIV** (**FIV**-pPPR), and two (-)-.beta.-L-2',3'-dideoxy-3'-thiacytidine- (**3TC**-) resistant mutants of **FIV**-pPPR. Sample Population-Peripheral blood mononuclear cells (PBMC) from 4 specific-pathogen free cats. Procedure-Two point mutations corresponding to mutations of human immunodeficiency virus type 1 (HIV-1) were engineered into the highly conserved YMDD motif of the reverse transcriptase-(RT-) encoding region of the **FIV**-pPPR pol gene. Replication kinetics and nucleoside analog susceptibilities of **FIV** -Maxam, **FIV**-pPPR, and the 2 mutant viruses were measured in vitro, using feline PBMC. Results-Replication kinetics and nucleoside analog susceptibilities were similar between **FIV**-Maxam and **FIV**-pPPR. However, **FIV**-Maxam was significantly more susceptible to **3TC**. A methionine-to-valine mutation at codon 183 (M183V) of the RT-encoding region of the pol gene of **FIV** -pPPR conferred high level phenotypic resistance to **3TC** and cross-resistance to the related compd. (-)-.beta.-L-2',3'-dideoxy-5-fluoro-3'-thiacytidine. Conclusions and Clin. Relevance-Similarities between **FIV**-Maxam and **FIV**-pPPR suggest that results of studies performed using **FIV**-pPPR will have relevance to natural **FIV** infection in cats. In vitro evaluation of nucleoside analog susceptibilities of **FIV**-Maxam may help det. concns. of nucleoside analogs required for effective treatment of **FIV** -infected cats. Impact for Human Medicine-**3TC** resistance of **FIV**-pPPR M183V was similar in magnitude to that of HIV-1 M184V, a mutant described in infected humans treated with **3TC**. Thus, **FIV**-pPPR M183V may be a useful model for studying the in vivo effects of **3TC** resistance on lentivirus pathogenesis.

ACCESSION NUMBER: 2001:301214 CAPLUS
DOCUMENT NUMBER: 135:343070
TITLE: In vitro characterization of **FIV**-pPPR, a pathogenic molecular clone of **feline immunodeficiency virus**, and two drug-resistant pol gene mutants
AUTHOR(S): Stevenson, M. A. McCrackin; McBroom, Douglas G.
CORPORATE SOURCE: Division of Biological Sciences, College of Arts and Sciences, University of Montana, Missoula, MT, 59812, USA
SOURCE: American Journal of Veterinary Research (2001), 62(4), 588-594
CODEN: AJVRAH; ISSN: 0002-9645
PUBLISHER: American Veterinary Medical Association
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI In vitro characterization of **FIV**-pPPR, a pathogenic molecular clone of **feline immunodeficiency virus**, and two drug-resistant pol gene mutants

AB Objective-To compare in vitro replication kinetics and nucleoside analog susceptibilities of a natural **feline immunodeficiency virus** (**FIV**) isolate (**FIV**-Maxam), a mol. clone of **FIV** (**FIV**-pPPR), and two (-)-.beta.-L-2',3'-dideoxy-

3'-thiacytidine- (**3TC**-) resistant mutants of **FIV**-pPPR. Sample Population-Peripheral blood mononuclear cells (PBMC) from 4 specific-pathogen free cats. Procedure-Two point mutations corresponding to mutations of human immunodeficiency virus type 1 (HIV-1) were engineered into the highly conserved YMDD motif of the reverse transcriptase-(RT-) encoding region of the **FIV**-pPPR pol gene. Replication kinetics and nucleoside analog susceptibilities of **FIV** -Maxam, **FIV**-pPPR, and the 2 mutant viruses were measured in vitro, using feline PBMC. Results-Replication kinetics and nucleoside analog susceptibilities were similar between **FIV**-Maxam and **FIV**-pPPR. However, **FIV**-Maxam was significantly more susceptible to **3TC**. A methionine-to-valine mutation at codon 183 (M183V) of the RT-encoding region of the pol gene of **FIV** -pPPR conferred high level phenotypic resistance to **3TC** and cross-resistance to the related compd. (-)-.beta.-L-2',3'-dideoxy-5-fluoro-3'-thiacytidine. Conclusions and Clin. Relevance-Similarities between **FIV**-Maxam and **FIV**-pPPR suggest that results of studies performed using **FIV**-pPPR will have relevance to natural **FIV** infection in cats. In vitro evaluation of nucleoside analog susceptibilities of **FIV**-Maxam may help det. concns. of nucleoside analogs required for effective treatment of **FIV** -infected cats. Impact for Human Medicine-**3TC** resistance of **FIV**-pPPR M183V was similar in magnitude to that of HIV-1 M184V, a mutant described in infected humans treated with **3TC**. Thus, **FIV**-pPPR M183V may be a useful model for studying the in vivo effects of **3TC** resistance on lentivirus pathogenesis.

ST **feline immunodeficiency virus** clone drug resistance pol gene

IT Drug resistance
(**3TC**; in vitro characterization of **FIV**-pPPR, a pathogenic mol. clone of **feline immunodeficiency virus**, and two drug-resistant pol gene mutants)

IT Cat (Felis catus)
Feline immunodeficiency virus
(in vitro characterization of **FIV**-pPPR, a pathogenic mol. clone of **feline immunodeficiency virus**, and two drug-resistant pol gene mutants)

IT Gene, microbial
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(pol; in vitro characterization of **FIV**-pPPR, a pathogenic mol. clone of **feline immunodeficiency virus** , and two drug-resistant pol gene mutants)

IT 7481-89-2, Ddc 30516-87-1, **Azt** 134678-17-4, **3Tc** 143491-54-7, Ftc
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in vitro characterization of **FIV**-pPPR, a pathogenic mol. clone of **feline immunodeficiency virus**, and two drug-resistant pol gene mutants to)

L4 ANSWER 12 OF 14 CAPLUS COPYRIGHT 2002 ACS

AB Methods are provided for therapeutic and prophylactic treatment of cats against **FIV** infection. Methods of the invention use a combination of antiretroviral compds. to treat or prevent **FIV** infection in a feline animal. In one embodiment, the method comprises administering an effective amt. of **AZT** and another nucleoside analog, e.g. **3TC**, to the animal. In another embodiment, cats are given an ED(s) of **AZT**, **3TC** and a retroviral

protease inhibitor.

ACCESSION NUMBER: 1999:763838 CAPLUS
DOCUMENT NUMBER: 132:431
TITLE: Combination therapy for treatment of **feline immunodeficiency virus** (**FIV**) infection
INVENTOR(S): Dunn, Ben M.; Yamamoto, Janet K.; Arai, Maki
PATENT ASSIGNEE(S): University of Florida, USA
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9960988	A2	19991202	WO 1999-US11940	19990528
WO 9960988	A3	20001207		

W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1146882	A2	20011024	EP 1999-926027	19990528

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

PRIORITY APPLN. INFO.: US 1998-87281P P 19980529
WO 1999-US11940 W 19990528

TI Combination therapy for treatment of **feline immunodeficiency virus** (**FIV**) infection

AB Methods are provided for therapeutic and prophylactic treatment of cats against **FIV** infection. Methods of the invention use a combination of antiretroviral compds. to treat or prevent **FIV** infection in a feline animal. In one embodiment, the method comprises administering an effective amt. of **AZT** and another nucleoside analog, e.g. **3TC**, to the animal. In another embodiment, cats are given an ED(s) of **AZT**, **3TC** and a retroviral **protease inhibitor**.

ST **FIV** antiviral combination nucleoside analog **AZT**; **AZT 3TC FIV** antiviral combination; retrovirus **protease inhibitor FIV** antiviral combination; **feline immunodeficiency virus** antiviral combination

IT Transplant and Transplantation
Transplant and Transplantation
(bone marrow; **feline immunodeficiency virus** combination therapy)

IT Antiviral agents
Drug interactions
Feline immunodeficiency virus
(**feline immunodeficiency virus** combination therapy)

IT Nucleoside analogs
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES

(Uses)
(**feline immunodeficiency virus** combination therapy)

IT Retroviridae
(**protease, inhibitors; feline immunodeficiency virus** combination therapy)

IT Drug interactions
(synergistic; **feline immunodeficiency virus** combination therapy)

IT Radiotherapy
(total body irradn.; **feline immunodeficiency virus** combination therapy)

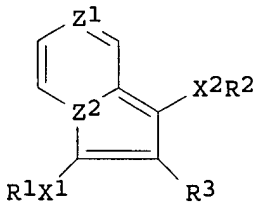
IT Bone marrow
Bone marrow
(transplant; **feline immunodeficiency virus** combination therapy)

IT 144114-21-6, Retropepsin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(HIV **protease inhibitors; feline immunodeficiency virus** combination therapy)

IT 30516-87-1, **AZT** 127779-20-8, Saquinavir 134678-17-4, **3TC** 137755-25-0, **HBY-793** 150378-17-9, Indinavir
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**feline immunodeficiency virus** combination therapy)

L4 ANSWER 13 OF 14 CAPLUS COPYRIGHT 2002 ACS

GI



I

AB A pharmaceutical compn. is provided for inhibiting replication of a retrovirus which comprises a compd. I (Z1 = CR5, N; Z2 = N; X1, X2 = O, S, NR4; R1-R5 = H, (un)branched C1-3 alkyl). Also provided is a pharmaceutical compn. for inhibiting replication of a retrovirus which comprises a first compd. which inhibits replication of the retrovirus and a second compd. having the above-defined structure. Methods are provided for inhibiting retroviral replication in a subject using the above compns. A pharmaceutical compn. is also provided for inhibiting tumor promoter-initiated transcription which comprises a compd. having the above-defined structure. Also provided is a method for preventing the formation of tumors in a subject which comprises administering the aforementioned compn. for inhibiting tumor-promoter initiated transcription. Oltipraz metabolite III prepn. and antiviral activity is

described. In ACH-2 cells, metabolite III was an effective inhibitor of PMA-induced HIV-1 replication. Oltipraz and metabolite III were synergistic in inhibiting HIV-1 replication.

ACCESSION NUMBER: 1997:204174 CAPLUS
DOCUMENT NUMBER: 126:195259
TITLE: Heterocyclic compounds, compositions, and methods for inhibiting replication of retroviruses and for inhibiting tumor promoter-initiated transcription
INVENTOR(S): Prochaska, Hans J.
PATENT ASSIGNEE(S): Sloan-Kettering Institute for Cancer Research, USA; Prochaska, Hans J.
SOURCE: PCT Int. Appl., 69 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9703055	A1	19970130	WO 1996-US11699	19960712
W: AU, CA, JP, MX, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9666767	A1	19970210	AU 1996-66767	19960712

PRIORITY APPLN. INFO.: US 1995-1110P P 19950713
WO 1996-US11699 W 19960712

OTHER SOURCE(S): MARPAT 126:195259

IT Antitumor agents
Antiviral agents
Drug delivery systems
Feline immunodeficiency virus
Feline leukemia virus
Human T-lymphotropic virus 1
Human immunodeficiency virus 1
Human immunodeficiency virus 2
Retroviridae
Transcription, genetic
Tumor promoters
(heterocyclic compds., compns., and methods for inhibiting replication of retroviruses and for inhibiting tumor promoter-initiated transcription)

IT 3056-17-5, D4T 7481-89-2, DDC 30516-87-1, **AZT** 69655-05-6, DDI 127779-20-8, Saquinavir 134678-17-4, **3TC** 157810-81-6, L-735524
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(heterocyclic compds., compns., combinations, and methods for inhibiting replication of retroviruses and for inhibiting tumor promoter-initiated transcription)

IT 9001-92-7, **Protease** 9068-38-6, Reverse transcriptase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors**; heterocyclic compds., compns., combinations, and methods for inhibiting replication of retroviruses and for inhibiting tumor promoter-initiated transcription)

L4 ANSWER 14 OF 14 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AB Autologous (auto-) and allogeneic (allo-) BMT of 18 **FIV**-infected and 20 uninfected cats were performed in our laboratory as an immune reconstitution therapeutic model for AIDS. Observation of auto-BMT of

FIV-infected cats revealed elevated **FIV** loads and low CD4/CD8 ratios following complete engraftment. In contrast, allo-BMT of infected cats had high mortality (1/12 or 8% survival) due to graft-versus-host disease, accelerated **FIV**-related disease, or their combination. Since successful engraftment, and survival were observed in allo-BMT of uninfected cats (10/14 or 71% survival), the high mortality in the infected cats was most likely caused by **FIV** infection. In order to decrease the **FIV** load, antiretroviral therapy was used in conjunction with auto-BMT (4 cats) and allo-BMT (6 cats) in some of these **FIV**-infected cats. Our previous studies using nucleoside reverse transcriptase inhibitors (NRTIs), **AZT** and **3TC**, demonstrated effective inhibition of in vitro **FIV** infections and effective prophylaxis in cats. In our current study, no decrease in **FIV** load was observed in cats receiving auto-BMT in combination with **AZT/3TC**. Moreover, one allo-BMT success occurred when combined with **AZT/3TC** treatments. This cat completely engrafted, maintained low **FIV** load and high CD4/CD8 ratio, and survived for more than 3 years until the study was concluded. In contrast, the remaining **AZT/3TC** -treated allo-BMT recipients succumbed to engraftment failure with severe wasting syndrome. These results are similar to the combined BMT/NRTIs therapeutic results of human AIDS patients. Although BMT for HIV disease remains controversial, the use of BMT in feline AIDS model should help identify a more effective method for using BMT as an immune reconstitution therapy for human AIDS.

ACCESSION NUMBER: 2001:258484 BIOSIS
DOCUMENT NUMBER: PREV200100258484
TITLE: Update on bone marrow-transplantation (BMT) of **FIV** -infected cats as an immune reconstitution therapeutic model for AIDS.
AUTHOR(S): Arai, Maki; Tanabe, Taishi; Pu, Ruiyu; Yamamoto, Janet K.
SOURCE: FASEB Journal, (March 8, 2001) Vol. 15, No. 5, pp. A1190. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
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IT Major Concepts
Immune System (Chemical Coordination and Homeostasis); Infection

IT Diseases
feline immunodeficiency virus infection:
immune system disease, transplantation treatment, viral disease

ORGN Super Taxa
Felidae: Carnivora, Mammalia, Vertebrata, Chordata, Animalia;
Retroviridae: Animal Viruses, Viruses, Microorganisms

ORGN Organism Name
cat (Felidae): animal model; **feline immunodeficiency virus** [**FIV**] (Retroviridae): pathogen

ORGN Organism Superterms
Animal Viruses; Animals; Carnivores; Chordates; Mammals; Microorganisms; Nonhuman Mammals; Nonhuman Vertebrates; Vertebrates; Viruses

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     (FILE 'HOME' ENTERED AT 00:08:56 ON 30 SEP 2002)

     INDEX 'ADISALERTS, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUASCI,
     BIOBUSINESS, BIOCOMMERCE, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA,
     CANCERLIT, CAPLUS, CEABA-VTB, CEN, CIN, CONFSCI, CROPB, CROPU, DDFB,
     DDFU, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, ...' ENTERED AT 00:09:08 ON
     30 SEP 2002
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               29   FILE MEDLINE
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                1   FILE PHAR
                2   FILE PHIN
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               39   FILE SCISEARCH
               36   FILE TOXCENTER
              228   FILE USPATFULL
                2   FILE USPAT2
               17   FILE VETU
               11   FILE WPIDS
               11   FILE WPINDEX
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     FILE 'DRUGU, EMBASE, LIFESCI, MEDLINE, CAPLUS, BIOSIS, BIOBUSINESS'
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L3             85 DUP REM L2 (112 DUPLICATES REMOVED)
L4             14 S L3 AND (3TC OR PROTEASE(2A)INHIBITOR? OR HBY(W)793)

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